UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

ABBOTT GMBH & CO., KG; ABBOTT BIORESEARCH CENTER, INC.; and ABBOTT BIOTECHNOLOGY LTD.,	)	
Plaintiffs,	)	**Civil Action No. 09-11340-FDS**
v.	)	
CENTOCOR ORTHO BIOTECH, INC., and CENTOCOR BIOLOGICS, INC.	)	
Defendants.	)	

MEMORANDUM AND ORDER ON
MOTION FOR JUDGMENT AS A MATTER OF LAW

SAYLOR, J.

This is a patent infringement action involving a class of antibodies developed to treat certain auto-immune diseases. Plaintiffs AbbVie Deutschland GmbH & Co., KG; AbbVie Bioresearch Center, Inc.; and AbbVie Biotechnology Ltd. (collectively "Abbott") and defendants Janssen Biotech, Inc. and Centocor Biologics, Inc. (collectively "Centocor") are pharmaceutical companies.[1] Abbott and Centocor have both developed antibodies capable of treating diseases associated with the overproduction of a naturally-occurring protein in the human body called interleukin-12 ("IL-12").

In 2009, Abbott brought suit seeking a judgment under 35 U.S.C. § 271 that its U.S.

[1] Nearly all of the parties have undergone name changes during the course of this litigation. AbbVie Biotechnology Ltd. was formerly known as Abbott Biotechnology Ltd.; AbbVie Deutschland GmbH & Co., KG was formerly known as Abbott GmbH & Co., KG; AbbVie Bioresearch Center, Inc. was formerly known as Abbott Bioresearch Center, Inc.; and Janssen Biotech, Inc. was formerly known as Centocor Ortho Biotech, Inc. For the sake of consistency and simplicity, the Court will continue to refer to plaintiffs as "Abbott," and defendants as "Centocor."

Patent No. 6,914,128 (the "'128 patent") and U.S. Patent No. 7,504,485 (the "'485 patent") are infringed by the drug Stelara, which Centocor manufactures. The case proceeded to trial in late 2012. At trial, Centocor did not contest the issue of infringement. Rather, it contested liability by contending that the asserted patent claims were invalid under 35 U.S.C. §§ 102, 103, and 112. Centocor raised four invalidity defenses: written description, enablement, obviousness, and anticipation.

Following an eleven-day jury trial, the jury returned a verdict that the claims at issue were invalid. They found invalidity on three independent bases: written description, enablement, and obviousness.[2] Abbott has filed a renewed motion for judgment as a matter of law on all three bases. For the reasons set forth below, Abbott's motion will be denied.

I. Background

The Court will assume familiarity with the facts and procedural background of this case, and will provide only a brief summary of the technology at issue.

This case involves a class of antibodies developed to treat diseases associated with the overproduction of interleukin-12, a naturally-occurring protein in the human body. When functioning properly, IL-12 assists the immune system by binding to receptors on the surfaces of certain cells as part of the body's inflammation response to infection. In some individuals, the body can over-produce IL-12, causing auto-immune diseases such as psoriasis. One way of treating such diseases is by inhibiting or blocking the effects of IL-12 through the use of antibodies. Antibodies are proteins that attach themselves to a target molecule—called an "antigen" for that antibody—by binding with a portion of that antigen called an "epitope." The

[2] The jury ruled in Abbott's favor on the issue of anticipation.

immune system produces antibodies that typically target antigens such as viruses, foreign bacteria, or other foreign substances, but an antibody may also target a non-foreign antigen such as IL-12.

The immune system naturally develops antibodies as a response to foreign antigens in the body. Because, however, IL-12 is a naturally-occurring human protein, the immune system does not naturally produce antibodies against it. Treatment of the over-production of IL-12 therefore requires the artificial creation of such antibodies. The subject matter of Abbott's '128 and '485 patents is a set of antibodies for IL-12. Likewise, Stelara contains an antibody developed by Centocor that also targets human IL-12.

There are multiple methods for creating antibodies to IL-12. Of these, two technologies allow the development of "fully human" antibodies that target human antigens with minimal risk of triggering adverse immune reactions. The first method, phage display technology, involves the use of bacteria that have been transfected with viral DNA that contains DNA corresponding to human antibody variable regions. The bacteria create viruses that have those variable regions expressed as proteins on their surfaces. The viruses that display antibody proteins with desired binding properties are screened (or "panned") by bringing them in contact with the target antigen and removing those that bind to it. The DNA encoding the corresponding antibody is then isolated and replicated. An antibody produced by this method is "recombinant," meaning that it is created by splicing and recombining DNA. This is the method used by scientists at Abbott to obtain the antibodies to IL-12 disclosed in the '128 and '485 patents.

The second method for producing human antibodies involves use of the immune system of a transgenic mouse. In a transgenic mouse, some of the genes that encode the mouse's

antibodies have been replaced with human antibody genes. When a human antigen such as IL-12 is introduced into a transgenic mouse, the mouse's immune system recognizes the antigen as foreign and develops antibodies that target it. Because the genes from which the transgenic animal's cells build the antibody are human, the resulting antibody will be appropriate for human patients. Antibodies with desired binding properties can then be reproduced using what is known as the hybridoma technique. This is the method used by scientists at Centocor to obtain the antibody to IL-12 known as Stelara.

II. Legal Standard

In a patent case, this Court analyzes a motion for judgment as a matter of law according to the law of the First Circuit. *August Tech. Corp. v. Camtek, Ltd.*, 655 F.3d 1278, 1281 (Fed. Cir. 2011).

A party that seeks to overturn a jury verdict "faces an uphill battle." *Monteagudo v. Asociacion de Empleados del Estado Libre Asociado de P.R.*, 554 F.3d 164, 170 (1st Cir. 2009). To grant judgment as a matter of law, the Court must determine that the "evidence points so strongly and overwhelmingly in favor of the moving party that no reasonable jury could have returned a verdict adverse to that party." *Malone v. Lockheed Martin Corp.*, 610 F.3d 16, 20 (1st Cir. 2010). All evidence presented to the jury, and all reasonable inferences drawn therefrom, must be viewed in the light most favorable to the verdict. *Osorio v. One World Techs., Inc.*, 659 F.3d 81, 84 (1st Cir. 2011). The jury's verdict should stand unless the evidence, viewed in such a favorable light, nonetheless "points unerringly to an opposite conclusion." *Zimmerman v. Direct Fed. Credit Union*, 262 F.3d 70, 75 (1st Cir. 2001).

At trial, all patents were presumed valid. To overcome that presumption, defendant was

required to present clear and convincing evidence of invalidity. Thus, the key question is whether a reasonable jury could have found that there was clear and convincing evidence that the patents were invalid.

III. Analysis

A. Written Description

1. Legal Standard

To satisfy the written description requirement, the disclosures in a patent specification must "clearly allow [a person] of ordinary skill in the art to recognize that the inventor invented what is claimed." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010). When the patent claims a genus, the specification must describe the invention in a way that makes it clear that the genus has been invented, not just a species of the genus. *Carnegie Mellon Univ. v. Hoffman-La Roche Inc.*, 541 F.3d 1115, 1124 (Fed Cir. 2008). This is particularly true when the patent claims a genus defined by functional language, because such claims run the risk of "simply claim[ing] a desired result . . . without describing species that achieve that result." *Ariad*, 598 F.3d at 1349.

The Federal Circuit has set forth two possible ways to claim a genus: a party may disclose either a "representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can 'visualize or recognize' the members of the genus." *Ariad*, 598 F.3d at 1350. Only the "representative species" test is at issue in this case.

There is no simple definition for what constitutes a "representative number of species." There are no "bright-line rules" governing the number of species that a patent must disclose in

order to satisfy the representative species test. Rather, it is a case-by-case question of whether "the species which are adequately described are representative of the entire genus." *Carnegie Mellon*, 541 F.3d at 1124. When there is substantial variation within the genus, one must describe "a sufficient variety of species to reflect the variation within the genus." *Id.* at 1124.

2. Jury Verdict on Written Description

The jury found by clear and convincing evidence that all five claims of the '128 patent and the '485 patent at issue in this case failed to meet the written-description requirement, and were therefore invalid. Plaintiff contends that there was not substantial evidence to support the jury's verdict, and that it is entitled to judgment as a matter of law on the question of written description.

The adequacy of the written description essentially turns on whether the patents disclosed sufficient representative species to support a claim to the genus. Plaintiff does not contend that defendant did not put forth evidence on this issue; rather, it challenges the relevance of defendant's evidence. Plaintiff essentially raises two different relevancy challenges. First, plaintiff asserts that the only evidence that defendant put forward to support its contention that the disclosed antibodies are not representative of other members of the genus was based on structural difference. Plaintiff contends that because the claims are functional, not structural, structural difference is irrelevant. Second, plaintiff asserts that defendant only put forward evidence of differences between the disclosed antibodies and the allegedly infringing product, Stelara. Plaintiff contends that this is the wrong inquiry; the patent must disclose species that are representative of the genus, not of the allegedly infringing product. Thus, plaintiff claims that this evidence is also irrelevant.

Plaintiff also raises a number of challenges to the legal test relied upon by defendant and the policy implications of allowing structural arguments. The Court will address each of these challenges in turn.

a. Structural Differences as Evidence of Non-Representativeness

The Court will evaluate plaintiff's first challenge to the sufficiency of defendant's evidence in three steps. First, the Court will briefly summarize the evidence of structural differences that was presented. Second, the Court will evaluate the relevance of those differences to the central question of whether the species disclosed in the patents were representative of the claimed genus. Third, the Court will summarize the evidence of similarity that was presented, in order to determine whether a reasonable jury could have concluded that the disclosed species were not representative.

Defendant introduced evidence that both the '128 and the '485 patent only disclose species that are closely related structurally, and thus do not disclose the full variety of the genus. The Court will not attempt to provide an exhaustive recounting of defendant's evidence in its entirety. Among other things, the jury heard testimony that:

- The disclosed species were all from the same "lineage" of antibodies, in that they were all created based on the Joe 9 antibody. (Siegel Tr. Day 5 at 15:4-9).
- There was a high percentage of sequence homology among the disclosed species, and a much lower percentage of sequence similarity between any of the disclosed species and Stelara. (Siegel Tr. Day 5 at 39:7-10).
- The most important regions of an antibody are the complementarity-defining regions, or "CDR regions." There were no examples in the patent of antibodies with the same CDR length as Stelara. (Siegel Tr. Day 5 at 39:11-13);
- Antibodies have different kinds of heavy chains. All antibodies disclosed in the patent have VH3 heavy chains. Stelara has a VH5 heavy chain. There were no examples disclosed in the patents of antibodies with VH5 heavy chains. (Siegel

Tr. Day 5 at 35:8-36:14).

- Antibodies have different kinds of light chains. All antibodies disclosed in the patent have lambda family light chains. Stelara has a kappa family light chain. There were no examples in the patent of antibodies with kappa family light chains. (Siegel Tr. Day 5 at 36:22-37:8).

- Antibodies bind to different epitopes on an antigen. There were no examples in the patent of antibodies that binds to the same epitope as Stelara. There was also some testimony that there is no overlap between the binding sites. (Eck Tr. Day 3 at 161:2-24).

The question then becomes whether the differences as to which defendant elicited testimony and introduced evidence are relevant to the representativeness of the disclosed species. Plaintiff contends that the only relevant characteristics in determining whether the disclosed antibodies are representative are those that were claimed—for instance, the K_{off} rate. Because the claims do not rely on any particular structure, plaintiff contends that the structural differences relied upon by defendant are irrelevant.

The relevance of these differences is a question of fact that was properly presented to the jury. Indeed, the jury heard significant testimony about the ways in which structure can effect function. For instance, the jury heard expert testimony that:

- the structure of an antibody relates to whether and where an antibody binds to a target antigen (Marks Tr. Day 9 at 152:18-153:1);

- antibodies that bind to different epitopes interact in different ways with the target antigen (Marks Tr. Day 9 at 152:14-17);

- the difference between a light chain in the kappa family and a light chain in the lambda family can affect an antibody's biological properties (Siegel Tr. Day 5 at 38:17-20).

The jury also heard expert testimony on the precise question of whether the disclosed antibodies were representative. Dr. Siegel presented his opinion that the disclosed antibodies

were not representative and that there was no way to predict the amino acid sequence of any other antibody falling within the scope of the claims based on what was disclosed in the patent. (Siegel Tr. Day 5 at 26:8-15, 39:23-41:17). Even plaintiff's expert, Dr. Marks, indicated that he had no idea how many antibodies would meet the scope of the claims. (Marks Tr. Day 9 at 52:9, 137:12-21). This evidence supports a reasonable inference that structure is relevant to the functional claims, and that the disclosed species were not representative.

Just as defendant set forth evidence of the relevance of structure and the non-representativeness of the disclosed species, plaintiff elicited testimony about the irrelevance of structure to the claims and the representativeness of the disclosed species. On the irrelevance of structure to the claims, plaintiff introduced evidence that some antibodies with significant structural similarity to the disclosed antibodies are nonetheless very different functionally. For example, although J695 bears a strong structural resemblance to Joe 9, only J695 is a disclosed antibody that meets the limitations of the claims; Joe 9 falls well outside of the functional requirements of the claims. On the question of representativeness, the jury heard testimony that the disclosed antibodies covered the full variation in the genus, based on claimed characteristics such as binding affinity. It also heard testimony that the patents disclosed numerous representative examples for each of the asserted claims; indeed, it was uncontested that they disclosed all of the known antibodies that meet each claim except for Stelara. (Siegel Tr. Day 5 at 136:19-137:25; Marks Tr. Day 9 at 48:2-51:19). Plaintiff's expert offered his opinion that the evidence demonstrated that the disclosed antibodies were representative. (Marks Tr. Day 9 at 57: 7-19).

Nonetheless, the evidence presented by plaintiff was not so overwhelming as to require a

conclusion of representativeness. Even given defendant's high standard of proof, the jury was free to discount plaintiff's evidence of similarity when compared with defendant's evidence of the differences between the disclosed antibodies and Stelara. It was also free to credit the opinions of defendant's experts over those of plaintiff's experts.

Reviewing the evidence in the light most favorable to the verdict, it was not unreasonable for the jury to conclude, based on the differences between the disclosed species and Stelara, that there was clear and convincing evidence that the patents had not disclosed species that fully reflected the variation in the genus. Accordingly, the jury could reasonably conclude that the written description requirement was not met.

b. Evidence that Stelara Was Not Represented

Plaintiff next contends that defendant improperly challenged the adequacy of the patents' written descriptions by arguing that the disclosed antibodies were not representative of Stelara, the infringing product. Plaintiff contends that the proper inquiry is whether the disclosed antibodies were representative of *the genus*, not of Stelara.

It is undisputed that Stelara falls within the claimed genus. Indeed, as discussed above, it is uncontested that Stelara is the only known antibody in the genus other than those disclosed in the patent. Thus, by presenting evidence that described the characteristics of Stelara, defendant was not simply comparing the disclosed antibodies to the infringing product. Rather, defendant was providing the jury with a fuller picture of the variety in the claimed genus. The jury was free to make the determination that Stelara was, in fact, fundamentally different from the disclosed antibodies. The jury was further free to make the reasonable inference that, if the claimed genus included an antibody that was fundamentally different from the disclosed

antibodies, the disclosed antibodies were not representative of the variety in the claimed genus. Based on that inference, it was not unreasonable for the jury to be persuaded by defendant's evidence comparing the disclosed species with Stelara.

c. Disclosure of Every Antibody Other Than Stelara

Plaintiff next contends that the jury's verdict imposes an unreasonable burden on plaintiff by holding the asserted claims invalid despite the patents' undisputed disclosure of every known antibody in each genus except for Stelara. Plaintiff contends that the standard imposed by the jury effectively eviscerates a patentee's ability to claim a genus by requiring disclosure of every species within the genus.

Plaintiff is correct that, even in an unpredictable art, there is no universal requirement that a patent disclose every species. *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1569 (Fed. Cir. 1997). Disclosed species may be representative even if they consist of only a small fraction of the total number of species in the genus. However, that is not to say that there are no circumstances under which the existence of an undisclosed species could call into question the representativeness of the disclosed species. Representativeness is a fact-intensive inquiry that is decided on a case-by-case basis. The key question is whether the disclosed species represent the *variety* in the genus.

Here, the jury accepted defendant's evidence that the disclosed species, while numerous, were nonetheless homogenous. Although only one other known species belongs to the genus, the jury implicitly found it to be substantially different from the disclosed species. Viewing this factual determination in the light most favorable to the verdict, the Court finds that it gives rise to a reasonable inference that the genus is much broader than the species disclosed by plaintiff

suggest. While a patent need not *always* disclose every species in order to claim a genus, it was not unreasonable for the jury to determine, based on the facts of this case, that plaintiff's disclosed species, while numerous, were not representative. Accordingly, the patent's disclosure of all but one known antibody in each genus is not a basis for disturbing the jury's verdict.

d. "Visualization and Recognition" Requirement

Plaintiff next contends that defendant's case relied on the incorrect legal standard for the representative species test.

The written description requirement, as set forth by the Federal Circuit, requires the specification to disclose:

> either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can "visualize or recognize" the members of the genus.

Ariad Pharmaceuticals, Inc. v. Eli Lilly & Co., 598 F.3d 1336, 1350 (Fed. Cir. 2010) (en banc). This language has been interpreted as setting forth two separate tests: a "representative species test" and a "structural features test." Plaintiff contends that the "visualize or recognize" language applies only to the structural features test, and that defendant's case inappropriately conflated the two.

The Federal Circuit has never explicitly held as much, and this Court finds that the case law is at best ambiguous. Neither *Ariad*, nor the case from which the language derives, *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997), indicate that the "visualize or recognize" requirement does not apply to the representative species test. Indeed, the court in *Ariad* went on to explain that the adequacy of a written description depends on

> a precise definition, such as by structure, formula, chemical name, physical properties, or other properties, of species falling within the genus sufficient to

> distinguish the genus from other materials . . . . We have also held that functional claim language can meet the written description requirement when the art has established a correlation between structure and function.

Ariad, 598 F.3d at 1350. This language seems to suggest that a genus could be recognizable based on properties other than structural characteristics. The disclosure of a representative number of species, representing the variety in the genus, is a means of distinguishing that genus from other materials, thus rendering it recognizable. There is Federal Circuit precedent to support this interpretation; the court considered structure in the context of the representative species test in *Carnegie Mellon Univ. v. Hoffman-La Roche Inc.*, 541 F.3d 1115 (Fed. Cir. 2008).

In the absence of any clear evidence that the jury relied on an incorrect interpretation of the law, the Court finds no basis for disturbing the jury's verdict.

e. Policy Consequences

Plaintiff next contends that allowing the jury's analysis of the representativeness of the disclosed species to become unmoored from the limitations of the claims is "an invitation to litigation-inspired distinctions that have no relation to the claims and no basis in science." (Pl. Br. at 13). Plaintiff suggests that future defendants could point to arbitrary distinctions, such as molecular weight or greater proportions of some types of amino acids than other kinds, to distinguish infringing embodiments from disclosed embodiments.

The Court need not evaluate such extreme possibilities in this case. Here, there is substantial evidence that there is a correlation between structure and function, and that the structural differences are therefore relevant to what is claimed. While it may be unpredictable *which* structure will lead to better or worse functional results, the jury heard testimony that structure has a significant effect on function. Indeed, both sides agree that one small change in

an amino acid sequence can totally change an antibody's functional characteristics. For precisely this reason, defendant's evidence that the structure of Stelara is different from the structure of the disclosed antibodies supports a reasonable inference that the patent does not disclose the variety of the genus, but "merely draw[s] a fence around the outer limits of the purported genus." *Ariad*, 598 F.3d at 1350.

Faced with a motion for judgment as a matter of law, this Court need not determine the policy consequences that might result in future cases from allowing a jury to hear evidence of distinctions that have no relation to the claims. Here, there was sufficient testimony about the relevance of structure to the claim limitations to establish a clear link between structure and function. Thus, there was sufficient evidence to support the jury's verdict that the disclosed antibodies were not representative of the claimed genus.

f. Summary

When viewed in the light most favorable to the verdict, the evidence supports the jury's conclusion on written description. Accordingly, plaintiff's motion for judgment as a matter of law on the issue of written description will be denied.

B. Enablement

1. Legal Standard

To meet the enablement requirement, a patent specification must "teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation." *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365 (Fed Cir. 1997). For composition claims, "the specification need teach only one mode of making and using a claimed composition." *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1335 (Fed

Cir. 2003). As is true for written description, the law imposes additional requirements when a patent claims a genus. In order to consider a patent enabled, a jury must determine that the specification enables a representative number of species falling within the scope of a genus. *See In re. Angstat*, 537 F.2d 498, 502-03 (C.C.P.A. 1976).

2. Jury Verdict on Enablement

Plaintiff's central challenge to the jury's verdict on enablement tracks closely with its central argument regarding written description. Specifically, plaintiff contends that the evidence showed that the patent enabled sufficient representative species for each asserted claim.

The uncontested evidence at trial demonstrated that the patents do not enable the production of Stelara. In particular, defendant presented evidence that the patents describe use of a particular phage-display library. (Siegel Tr. Day 5 at 44:3-25). That phage-display library was only able to create antibodies with VH1, VH3, and VH4 heavy chains. (Siegel Tr. Day 5 at 43:22-44:25). Thus, an antibody like Stelara, with a VH5 heavy chain, could not be created from the phage-display library described in the patent, and was therefore not enabled. (Siegel Tr. Day 5 at 45:1-7).

It is uncontested that the patent enables all of the disclosed species. Accordingly, plaintiff's challenge to the jury's verdict on enablement essentially asks again whether the jury could reasonably have determined, by clear and convincing evidence, that the disclosed species were not representative. For the same reasons set forth in the written-description analysis, it was reasonable for the jury to conclude from the evidence regarding differences between the disclosed species and Stelara that the disclosed species were not representative. When combined with the fact that the patent did not enable any antibodies like Stelara, this conclusion supports

the jury's determination that the patent did not enable the full scope of the claimed invention.

Plaintiff also contends that defendant incorrectly argued that the patents were required to enable antibodies made by transgenic mice. This challenge appears to misunderstand defendant's argument. While a patent need only teach a single way of making and using the composition, it must provide at least one way of making and using *the full scope* of the genus. Defendant does not suggest that the patents needed to teach a person of ordinary skill in the art how to make human antibodies using transgenic mice. Rather, defendant suggests that the full scope of the genus includes antibodies like Stelara; thus, to enable the full scope of the genus, defendant asserts that the patent must teach a way to make an antibody like Stelara. Once again, this argument turns on whether the disclosed species represented the full scope of the claimed antibodies. As discussed above, a reasonable jury could conclude that they did not.

Accordingly, defendant's motion for judgment as a matter of law on the issue of enablement will be denied.

C. Obviousness

1. Legal Standard

An invention cannot be patented if the subject matter would have been obvious at the time of the invention. A claim is invalid for obviousness if "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103(a). To challenge a patent as obvious, one must prove, by clear and convincing evidence, that a person of ordinary skill in the art (1) would have been motivated to combine the teachings of the prior art references to achieve the claimed invention and (2) would

have had a reasonable expectation of success in doing so. *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009). A reasonable expectation of success does not require absolute predictability. *In re Droge*, 695 F.3d 1334, 1338 (Fed. Cir. 2012).

One method of proving an invention obvious is by proving it was "obvious to try." To do so, a party must demonstrate that: (1) there was evidence of a design need or market pressure to solve a problem and a finite number of identified, predictable solutions; and (2) a person of ordinary skill in the art both would have anticipated success and actually achieved it. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007).

When a patent claims a genus, an invention is obvious if a single embodiment falling within the scope of the claims is obvious. *Cf. Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1300 (Fed. Cir. 2007).

Obviousness is a question of law based on underlying factual findings. On a motion for judgment as a matter of law, the underlying findings of fact—both explicit and implicit—are reviewed for substantial evidence. Those findings include (1) the scope and content of the prior art; (2) differences between the prior art and the claimed invention; and (3) the level of ordinary skill in the art. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966).[3] The ultimate legal conclusion is reviewed without deference on the conclusion of obviousness.

2. Jury Verdict on Obviousness

The first step in the Court's obviousness analysis is to review the jury's findings of fact to determine whether the verdict is supported by substantial evidence. The question of

[3] Secondary considerations are also typically reviewed as findings of fact. However, none are relevant here.

obviousness was submitted to the jury without specific interrogatories. Neither party requested any other course of action; indeed, both parties submitted proposed jury verdict forms that did not include interrogatories or otherwise request specific factual findings. Accordingly, the verdict form submitted to the jury asked for a verdict on the ultimate issue of obviousness with respect to each claim at issue, without requiring specific factual findings.

Having not asked for any explicit findings of fact on the factual underpinnings of the obviousness inquiry, Abbott now asks the Court to review these facts separate and apart from the verdict as a whole. Given the circumstances, the best method for doing so is far from clear; nonetheless, the Court will review the evidence supporting the jury's implicit findings of fact as an initial step in reviewing the verdict as to obviousness.

The Court will begin with the jury's conclusion that the patent claims were obvious, and then identify the factual determinations that necessarily underpin that conclusion. The Court will evaluate whether those factual findings were supported by substantial evidence at trial. The Court will then undertake review of the conclusion of obviousness as a matter of law.

a. Factual Findings

The factual elements that underlie the question of obviousness are (1) the scope and content of the prior art; (2) differences between the prior art and the claimed invention; and (3) the level of ordinary skill in the art. *Graham v. John Deere*, 383 U.S. 1, 17-18 (1966). The parties agreed in advance of trial that a person of ordinary skill in the art "is someone who had an

M.D. or Ph.D. in molecular biology, immunology, biophysics, biochemistry, or a related discipline, similar degree, or equivalent experience, and at least a few years of post-doctoral

experience working in the relevant art or the field of antibody engineering technology." The jury was instructed on this definition. Thus, the Court need not review any factual determinations as to the level of ordinary skill in the art.

i. Scope and Content of the Prior Art

Defendant's expert, Dr. Siegel, testified at some length about relevant references in the prior art. These references fell into three general categories: prior art regarding antibodies to IL-12, prior art regarding the use of transgenic mice, and prior art regarding phage display.

On the topic of antibodies to IL-12, Dr. Siegel testified to the following:

- it was known prior to 1999 that excess quantities of IL-12 could cause a person to suffer from certain auto-immune diseases (Siegel Tr. Day 5 at 49:18-23);
- the Strober patent described an example of treating certain diseases in humans—namely inflammatory bowel disease—using a humanized antibody to IL-12 in a pharmaceutically compatible carrier (Siegel Tr. Day 5 at 50:1-51:9);
- the Trinchieri patent discussed the use of antibodies that connect to the p40 sub-unit of IL-12, separately referring to both mouse antibodies that neutralize IL-12 and human antibodies (Siegel Tr. Day 5 at 52:8-53:14);
- the Meager article described that there are people with a neurological disorder who were able to make neutralizing human antibodies to IL-12 (Siegel Tr. Day 5 at 53:18-54:15).

The jury also heard testimony that the final reference, the Meager article, was not before the Patent & Trademark Office when the patent issued.

On the topic of prior art regarding transgenic mice, Dr. Siegel summarized the state of the prior art as of 1999 as follows:

- Kohler and Milstein had developed the hybridoma process in the 1970s (Siegel Tr. Day 5 at 57:2-9);

- scientists knew how to use transgenic mice to make human antibodies (Siegel Tr. Day 5 at 58:6-11);

- the Mendez article described (1) how to make transgenic mice; (2) the mice's ability to generate high-affinity fully human antibodies to multiple antigens, including human proteins; and (3) association constants in the same range as those disclosed in the patents. The same article reported that transgenic mice could be used to make high-affinity human antibodies against any human antigen (Siegel Tr. Day 5 at 59:2-63:6);

- the Kucherlapati '735 patent referred to earlier publications that described how to make transgenic mice, and described how to make human antibodies from transgenic mice. The patent also set forth a list of antigens for which human antibodies could be made, including IL-12 (Siegel Tr. Day 5 at 63:7-66:3);

- the Kucherlapati '584 patent described construction of a transgenic mouse, and stated that such mice could be used to make human antibodies to a large number of antigens, including IL-12. (Siegel Tr. Day 5 at 66:4-25).

On the topic of prior art regarding phage display, Dr. Siegel testified to the following:

- the '128 patent states that methodologies for preparing and screening antibody libraries were known in the art (Siegel Tr. Day 5 at 68:9-12);

- the Burton and Barbas article provided a summary of the field of phage display in 1994. It discussed how to use phage display to produce human antibodies in the lab from patients who have made antibodies to human proteins. It further suggested that one could use this means to construct a human antibody to IL-12. The article also discussed ways of improving the features of an antibody created through phage display, including ways of improving affinity or K_{off} (Siegel Tr. Day 5 at 68:18-73:6);

- the Schier article showed a process of editing small sequences of amino acids in the CDR regions, and then testing the KD, K_{off}, and K_{on} rates that resulted from the changes. The article also disclosed similar K_{off} rates to those claimed in the patents (Siegel Tr. Day 5 at 73:9-77:9).

Dr. Siegel summarized the importance of these prior art references by giving his opinion that, in 1999, a person of ordinary skill in the art (1) understood the difficulty of having excessive levels of IL-12 in a human body; (2) knew that antibodies could neutralize IL-12; (3)

knew that human antibody genes could encode neutralizing human antibodies to IL-12; (4) knew that phage display technologies were available for getting initial hits, and that there were methods for improving the antibodies for characteristics like affinity; (5) knew that transgenic mice were also available to make antibodies, and could create antibodies with low koff rates.

To reach its verdict, the jury must have credited this evidence as sufficient to provide a person of ordinary skill in the art with the motivation to attempt to combine the teachings of the prior art references to make a human, high-affinity, neutralizing antibody to IL-12. There is substantial evidence to support these determinations, and the Court therefore accepts them as true.

ii. Differences Between the Prior Art and the Claimed Invention

There are two significant differences between the prior art and the claimed invention. First, the prior art did not disclose a human antibody that binds to and neutralizes IL-12 that had a K_{off} rate in the range set forth in the claims—all the K_{off} rates in the prior art that match those for the claimed IL-12 antibodies correspond to other antigens. Second, the prior art did not disclose that non-diseased human DNA could provide code for building antibodies to IL-12.

The jury's verdict indicates that they implicitly found that these differences were not significant. The jury implicitly credited defendant's evidence that the state of the science was such that a person of ordinary skill in the art would have expected that, even with these differences, they could nonetheless achieve the desired K_{off} rates from non-diseased human DNA using the methodology discussed in the prior art.

The jury also implicitly credited defendant's portrayal of the likelihood of success. Dr. Siegel testified that the prior art revealed four different ways to affinity-mature an antibody to

improve its functional characteristics, including its K_{off} rate. He further testified that, based on all the prior art disclosed, it was his opinion that achieving a successful result in creating an antibody that neutralized IL-12 was predictable.[4] Defendant also called a witness, Dr. John Ghrayeb, who was qualified as a person of ordinary skill in the art, and who was involved in the creation of Stelara. Dr. Ghrayeb testified that he was very confident that their work would succeed. (Ghrayeb Tr. Day 2 at 90:1-12).

Plaintiff contends that this finding is undermined by undisputed testimony about antigen-to-antigen unpredictability. However, substantial evidence supported the jury's factual finding that there were predictable methods for getting *some* antibody that fell within the claims, even if the exact characteristics of that antibody could not be predicted. Defendant's expert's testimony that changing a single amino acid could affect the antibody's functional characteristics is not to the contrary. When a claim is functional, a person of ordinary skill in the art need not predict the structure of the embodiment—they simply must know how to use the methodology to achieve the functional result.

Plaintiff's reliance on the testimony of Jill Giles-Komar indicating that she did not have an expectation of success is similarly irrelevant. Ms. Giles-Komar was not, at the time, a person of ordinary skill in the art as the term was defined by the parties. Thus, what she may or may not have expected has no bearing on the legal question of obviousness.

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[4] Plaintiff correctly points out that the legal test for obviousness requires "anticipated success," rather than predictability. Dr. Siegel did not offer any opinion that referred specifically to "anticipated success." However, because the ultimate legal determination on the question of obviousness rests with this Court, it is of no consequence that defendant's experts did not set forth the precise legal test. The correct considerations were set forth in the jury's instructions, and Dr. Siegel's testimony was sufficiently clear to allow the jury to make a factual finding regarding how likely a person of ordinary skill in the art would have thought it was that he or she would achieve the desired result.

Plaintiff also contends, correctly, that its own expert testified that a person of ordinary skill in the art would not have had a reasonable expectation of success. However, determinations of fact and credibility are left to the jury. The jury was entitled to believe the testimony of defendant's experts over that of plaintiff's experts. Based on the jury's verdict, the Court infers that they credited defendant's experts on the question of the likelihood of success. The Court finds that there was substantial evidence to support their factual finding, and defers to them on that determination.

b. Legal Conclusion of Obviousness

Having found that the jury's implicit factual findings are supported by substantial evidence, the Court undertakes its own analysis of the legal conclusion.

In the context of a claim that an invention was obvious to try, there are two parts to the legal test of obviousness. To prevail, a defendant must demonstrate, by clear and convincing evidence, that (1) there was a design need or market pressure to solve a problem and a finite number of identified, predictable solutions, and (2) a person of ordinary skill in the art both anticipated success and actually achieved it.

Based on the jury's implicit factual findings, the Court concludes that there was clear and convincing evidence of a need to create a human, neutralizing, high-affinity antibody to IL-12. A person of ordinary skill in the art at the time knew that the overproduction of IL-12 was causing diseases, and that an antibody that neutralized IL-12 could be therapeutic. There were also a small number of identifiable solutions being used at the time to create antibodies to human antigens—namely phage display and transgenic mice. In addition, there was market pressure to create human antibodies, as opposed to humanized, chimeric, or mouse antibodies, as they were

more likely to be successfully marketed. Put together, these factors create a market need for a human antibody to IL-12, and a finite number of ways to achieve that goal.

There was also clear and convincing evidence that a person of ordinary skill in the art at the time could both anticipate success and actually achieve it. There is no question that both Abbott and Centocor had achieved success by 1999. Thus, the key question is whether a person of ordinary skill in the art would have anticipated that success. In concluding that such a person would have anticipated success, the Court places particular emphasis on the functional nature of the claimed result. It is not dependent on the particular amino acid sequence, or the use of any specialized methodology. If any one method of achieving any single embodiment would have caused a person of ordinary skill in the art to anticipate success, that is sufficient to render the invention obvious.

Based on the evidence and the jury's factual findings, the Court finds that there was a reasonable expectation of success using transgenic mice. Defendant's witness John Ghrayeb testified that he was so confident the mice could make the IL-12 antibody that he put his reputation on the line. Jill Giles-Komar testified that, of the three antigen targets to which Centocor devoted a committed research effort using transgenic mice, they were able to achieve high-affinity, neutralizing antibodies for all three. (Giles-Komar Tr. Day 3 at 90:18-25). The jury's implicit findings of fact credit this testimony. Thus, the Court concludes that there was a reasonable expectation that the use of transgenic mice would produce an antibody covered by the claims. Because the obviousness of any single method renders the claim obvious, the Court need

not evaluate the expectation of success using phage display.[5]

Accordingly, defendant's motion for judgment of a matter of law on the issue of obviousness will be denied.

IV. Conclusion

For the reasons stated above, defendant's motion for judgment as a matter of law is DENIED.

So Ordered.

/s/ F. Dennis Saylor
F. Dennis Saylor IV
United States District Judge

Dated: March 8, 2013

[5] Defendant has also moved for judgment as a matter of law on the basis that defendant's expert's testimony relied on prior art that was no more material than the prior art that was before the patent office. That issue will be addressed in substance in the Court's denial of defendant's motion for a new trial, and the motion will be denied here on similar grounds.